

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 16 May 2001 (16.05.01)	
International application No. PCT/US00/24745	Applicant's or agent's file reference X13288CPCT
International filing date (day/month/year) 11 September 2000 (11.09.00)	Priority date (day/month/year) 20 September 1999 (20.09.99)
Applicant HOCK, Janet, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:

07 March 2001 (07.03.01)

☐ in a notice effecting later election filed with the International Bureau on:
2. The election ☒ was
☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Pascal Piriou Telephone No.: (41-22) 338.83.38
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From the

INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

RECEIVED

by fax and post

To:

FEB 21 2002

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WEBSTER, Thomas D.
 ELI LILLY AND COMPANY
 Lilly Corporate Center
 Indianapolis, Indiana 46285
 ETATS-UNIS D'AMERIQUE

ELI LILLY & COMPANY
 PATENT DIVISION

NOTIFICATION OF TRANSMITTAL OF
 THE INTERNATIONAL PRELIMINARY
 EXAMINATION REPORT
 (PCT Rule 71.1)

FAX: 317 276 3861

Date of mailing
 (day/month/year)

25.02.2002

Applicant's or agent's file reference
 X-13288

IMPORTANT NOTIFICATION

International application No.
 PCT/US00/24745

International filing date (day/month/year)
 11/09/2000

Priority date (day/month/year)
 20/09/1999

Applicant

ELI LILLY AND COMPANY et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/



European Patent Office
 D-80288 Munich
 Tel. +49 89 2399 - 0 Tx: 523656 epmu d
 Fax: +49 89 2399 - 4465

Authorized officer

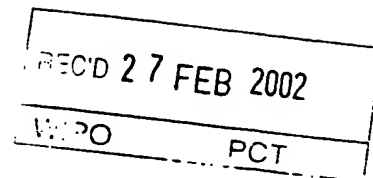
Cleere, C

Tel. +49 89 2399-7713



PATENT COOPERATION TREATY

PCT



INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference X-13288	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/24745	International filing date (day/month/year) 11/09/2000	Priority date (day/month/year) 20/09/1999	
International Patent Classification (IPC) or national classification and IPC G01N33/68			
Applicant ELI LILLY AND COMPANY et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☐ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☒ Certain documents cited
- VII ☒ Certain defects in the international application
- VIII ☒ Certain observations on the international application

Date of submission of the demand 07/03/2001	Date of completion of this report 25.02.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Cuendet, P Telephone No. +49 89 2399 8690 <div style="text-align: right;"> </div>

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24745

I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17):*)

Description, pages:

1-84 as originally filed

Claims, No.:

1-46 as originally filed

Drawings, sheets:

1/34-34/34 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/US00/24745

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-26.

because:

☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):

☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1-26 are so unclear that no meaningful opinion could be formed (*specify*):
see separate sheet

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/24745

- ☐ paid additional fees.
 - ☐ paid additional fees under protest.
 - ☒ neither restricted nor paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is
- ☐ complied with.
 - ☐ not complied with for the following reasons:
4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:
- ☐ all parts.
 - ☒ the parts relating to claims Nos. 1-26.

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/24745

1). Preamble

Invention 1 (claims 1-26, see below in point IV.):

In contrast to the statement in the description on p.3, lines 30 to p.4, line 18, the sole use of biological markers suitable for determining the course of therapy with parathyroid hormone (PTH) was well known in the art. The documents cited in the search report, **D1**: Cosman et al. (1998), **D2**: Hodsman et al. (1997), **D4**: Hodsman et al (1993) and **D5**: Brahm et al. (1994) are using biological markers as indicated in the examples of the present description* for determining the course of therapy with PTH.

*)see, e.g. the paragraph "Criteria for Evaluation" in examples

2). Point III.

Invention 1: no opinion regarding novelty, inventive step and industrial applicability for claims 1-26.

Claim 1

The correlation of the vague expressions "a level", "a product", "or combination thereof" together with the phrases "in a biological sample***", "correlating the level" renders the subject-matter of claim 1 so unclear that no statement regarding novelty, inventive step and industrial applicability can be given.

**)the skilled person would have known that the 2 "products" which have to be determined cannot be determined in the same biological sample, cf. "serum and urinary sampling" in e.g. D1

Claim 26

The correlation of the vague expressions "a level", "a product", "a reagent", "or combination thereof" renders the subject-matter of claim 26 so unclear that no statement regarding novelty, inventive step and industrial applicability can be given.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/US00/24745

3). **Point IV.**

The subject-matter of the claims of the present application would appear to relate to the following 3 inventions:

invention 1: monitoring the effects of administration of a parathyroid hormone to a subject by employing biological markers (claims 1-26);

invention 2: monitoring the effects of administration of a parathyroid hormone to a subject by X-ray absorptiometry (for the determination of the bone mineral density) together with a change in a biological marker (claims 27-37);

invention 3: compositions for currently reducing the risk of both vertebral and non-vertebral bone fracture in a male human subject at risk of or having osteoporosis, comprising a parathyroid hormone, without concurrent administration of an antiresorptive agent other than vitamin D or calcium (claims 38-46).

4). **Point VI.**

It is assumed that the claimed priority of 20.09.99 is valid. Thus document **D7:** WO-A-00/10596 would not belong to the prior art.

5). **Point VII.**

5.1. The description of the application as filed ends with the phrase "...the steps of:", cf. applicant's p.82 (Phoenix p.84).

5.2. In the description, the relevant prior art documents cited in the search report are neither indicated nor acknowledged.

6). **Point VIII.**

Invention 1: both independent claims 1 and 26 are unclear.

Claim 1: the correlation of the vague expressions "a level", "a product", "or combination thereof" together with the phrases "in a biological sample", "correlating the level" renders the subject-matter of claim 1 unclear.

Claim 26: the correlation of the vague expressions "a level", "a product", "a reagent", "or combination thereof" renders the subject-matter of claim 26 unclear.

PATENT COOPERATION TREATY

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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 3797.43W0U3	FOR FURTHER ACTION <small>see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.</small>	
International application No. PCT/US 00/ 24745	International filing date (day/month/year) 11/09/2000	(Earliest) Priority Date (day/month/year) 20/09/1999
Applicant ELI LILLY AND COMPANY		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☒ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

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☐ None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-37

Monitoring the effects of administration of a parathyroid hormone to a subject by determining levels of markers of bone formation, resorption and/or turnover.

2. Claims: 38-46

Compositions for concurrently reducing the risk of both vertebral and non-vertebral bone fracture in a male human subject at risk of or having osteoporosis, comprising a parathyroid hormone consisting of amino acid sequence 1-34 of human parathyroid hormone, without concurrent administration of an antiresorptive agent other than vitamin D or calcium.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates to a method for monitoring effects of administration of a parathyroid hormone by determining levels of one or more markers of an activity of this hormone. Suitable markers of bone formation include one or more enzymes indicative of osteoblastic processes of bone formation, preferably bone specific alkaline phosphatase, and/or one or more products of collagen biosynthesis, preferably a procollagen I C-terminal propeptide. Suitable markers of bone resorption and turnover include one or more products of collagen degradation, preferably an N-terminal telopeptide (NTX). In addition, methods for concurrently reducing the risk of both vertebral and non-vertebral bone fracture in a male human subject at risk of or having osteoporosis are disclosed, involving administration of human parathyroid hormone (amino acid sequence 1-34) without concurrent administration of an antiresorptive agent other than vitamin D or calcium.

**Published:**

- *With international search report.*
- *Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Intern: Application No

PCT/US 00/24745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68 A61K38/29 A61P19/10 C12Q1/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>COSMAN FELICIA ET AL: "Alendronate does not block the anabolic effect of PTH in postmenopausal osteoporotic women." JOURNAL OF BONE AND MINERAL RESEARCH, vol. 13, no. 6, June 1998 (1998-06), pages 1051-1055, XP000982943 ISSN: 0884-0431 the whole document</p> <p style="text-align: center;">--- -/--</p>	1-37

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search

16 February 2001

Date of mailing of the international search report

26/02/2001

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Hart-Davis, J

INTERNATIONAL SEARCH REPORT

Inter Application No

PCT/US 00/24745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HODSMAN A B ET AL: "A randomized controlled trial to compare the efficacy of cyclical parathyroid hormone versus cyclical parathyroid hormone and sequential calcitonin to improve bone mass in postmenopausal women with osteoporosis."</p> <p>JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 82, no. 2, 1997, pages 620-628, XP000982964 ISSN: 0021-972X the whole document</p> <p>---</p>	1-9,13, 14, 21-27, 34-37
X	<p>FINKELSTEIN JOEL S ET AL: "Prevention of estrogen deficiency-related bone loss with human parathyroid hormone-(1-34): A randomized controlled trial."</p> <p>JAMA (JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION), vol. 280, no. 12, pages 1067-1073, XP000982932 ISSN: 0098-7484 the whole document</p> <p>---</p>	1-9,13, 14, 23-27, 34-37
X	<p>HODSMAN ANTHONY B ET AL: "An evaluation of several biochemical markers for bone formation and resorption in a protocol utilizing cyclical parathyroid hormone and calcitonin therapy for osteoporosis."</p> <p>JOURNAL OF CLINICAL INVESTIGATION, vol. 91, no. 3, 1993, pages 1138-1148, XP000986523 ISSN: 0021-9738 the whole document</p> <p>---</p>	1,10-20, 23-34
X	<p>BRAHM H ET AL: "Effects of infusion of parathyroid hormone and primary hyperparathyroidism on formation and breakdown of type I collagen."</p> <p>CALCIFIED TISSUE INTERNATIONAL, vol. 55, no. 6, 1994, pages 412-416, XP000982970 ISSN: 0171-967X the whole document</p> <p>---</p>	1,10-20, 26-34
	<p>---</p> <p>-/--</p>	

INTERNATIONAL SEARCH REPORT

Intern I Application No
US 00/24745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SLOVIK DM, ROSENTHAL DI, DOPPELT SH, POTTS JT JR, DALY MA, CAMPBELL JA, NEER RM: "Restoration of spinal bone in osteoporotic men by treatment with human parathyroid hormone (1-34) and 1,25-dihydroxyvitamin D" JOURNAL OF BONE AND MINERAL RESEARCH, vol. 1, no. 4, August 1986 (1986-08), pages 377-381, XP000981712 the whole document	38-46
P,X	WO 00 10596 A (HOCK JANET M ;LILLY CO ELI (US)) 2 March 2000 (2000-03-02) cited in the application page 46, line 25 - line 30; example 3	1-37
P,X	KURLAND ETAH S ET AL: "Parathyroid hormone as a therapy for idiopathic osteoporosis in men: Effects on bone mineral density and bone markers." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 85, no. 9, September 2000 (2000-09), pages 3069-3076, XP000982939 ISSN: 0021-972X the whole document	1,13,14, 21-27, 34,38-46

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-37

Monitoring the effects of administration of a parathyroid hormone to a subject by determining levels of markers of bone formation, resorption and/or turnover.

2. Claims: 38-46

Compositions for concurrently reducing the risk of both vertebral and non-vertebral bone fracture in a male human subject at risk of or having osteoporosis, comprising a parathyroid hormone consisting of amino acid sequence 1-34 of human parathyroid hormone, without concurrent administration of an antiresorptive agent other than vitamin D or calcium.

INTERNATIONAL SEARCH REPORT
Information on patent family members

Application No
PCT/US 00/24745

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0010596 A	02-03-2000	AU 5575099 A EP 1059933 A NO 20005947 A	14-03-2000 20-12-2000 24-11-2000
<hr/>			